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EC CARDIOLOGY
Review Article

Patent Arterial Duct by Premature Infants - Changing Therapeutic Approaches

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Received: September 09, 2019; **Pubished:** September 27, 2019

Abstract

Clear guidelines for the most suitable therapeutic approach by premature infants with hemodynamically significant patent arterial duct are not available yet and the topic remains controversial. The transition between beneficial effects of additional ductal flow to deleterious sequelae needs to be better refined. There is a gradual shift from more aggressive and sometimes invasive treatment options to more conservative "watchful waiting" strategy the efficacy and safety of which need to be established.

Keywords: *Patent Arterial Duct; Hemodynamic Significance; Premature Infants; Treatment; Expectant Management*

Abbreviations

BPD: Broncho-Pulmonary Dysplasia; CLD: Chronic Lung Disease; COX: Cyclooxygenase; DA: Arterial Duct; ELBW: Extremely Low-Birth Weight; ERT: Early Treatment Group; GA: Gestational Age; hsPDA: Hemodynamically Significant Patent Arterial Duct; IVH: Intraventricular Hemorrhage; NEC: Necrotizing Enterocolitis; PDA: Patent Arterial Duct; PGE2: Prostaglandin E2; PVR: Pulmonary Vascular Resistance

Introduction

The arterial duct is a crucial component of the fetal circulation. It is a blood vessel which connects the pulmonary artery with the descending aorta and diverts right ventricular output away from the high-resistance lungs towards the low-resistance placenta. The factors which keep the DA open during fetal life are PGE2 produced in the placenta and low oxygen tension by the fetus.

Within hours after birth DA undergoes functional closure - it constricts in response to increased oxygen tension after expansion of the lungs and reduced levels of prostaglandin PGE2 as a result of enhanced catabolism [1]. The second phase is anatomical closure which finds place in the first three days of life by the full term infant as a result of structural remodeling of the duct.

By premature infants the duct is more sensitive to the vasodilating action of PGE2 and less sensitive to the postnatal rise in oxygen concentrations. PDA is defined as failure of the duct to constrict within 72 hours postnatal age. The frequency of PDA is inversely proportional to the GA and weight. At the 4th day of life DA remains open in approximately 10% of infants with GA 30 - 37 weeks, in 80% of the babies with GA 25 - 28 weeks, and in 90% of those with GA 24 weeks [2]. By postnatal age of 7 days these percentages decline to 2, 65 and 87%, respectively.

Spontaneous ductal closure is often seen by babies with GA > 28 weeks and with birth weight >1000g. By infants born before 27 gestational week the arterial ducts remains patent for weeks. By premature babies (GA < 27 weeks or birth weight < 1000g) who have PDA at the time they leave the hospital, the rate of spontaneous ductal closure is approximately 75%.

Hemodynamic significance of PDA

Is is well known that hsPDA can have deleterious consequences for the premature infant. Soon after birth the PVR is still high and the left-to-right shunting through the duct is limited. The physiologic fall in PVR by the neonate leads to increased blood flow via PDA and the direction of the shunting changes gradually from right-to left through bidirectional and to entirely left-to right - from the aorta to the pulmonary artery. The result is increased venous return to the left atrium, dilation of the left atrium and left ventricle, reduced systemic output and stealing of blood flow from the cerebral and the abdominal circulation.

Premature infants with significant left-to-right ductal shunting are at risk for serious complications due to the pulmonary overflow and systemic hypoperfusion - pulmonary edema, pulmonary hemorrhage, cerebral hypoxia, hepatic failure, renal insufficiency and NEC [3].

Although the presence of PDA can be suspected based on history of prematurity, typical auscultatory findings, chest X-ray with pulmonary hypervolemia and inability to wean from the ventilator, the most reliable method allowing direct visualization of the duct is echocardiography. There are numerous parameters which can be used in order to determine the hemodynamic significance of the PDA - ductal diameter >/= 1.5 mm, left atrium/aorta ratio > 1.5/1, left ventricular dilatation and reversed diastolic flow in the descending aorta or in the renal or in the cerebral arteries.

Only after PDA is defined as hemodynamically significant the need and type of treatment can be determined. When the shunting through the duct does not lead to any remarkable cardiopulmonary repercussions conservative management with fluid restriction and adjustment of the ventilation parameters is the first step.

Medical treatment of PDA

If despite the conservative measures the hemodynamic consequences of the PDA remain significant medical treatment can be considered. COX-inhibitors (indomethacin and ibuprofen) are used and over the last years there has been growing experience with paracetamol.

At some institutions prophylactic COX-inhibitors are applied to all premature babies independent of the presence or absence of PDA at the start of treatment. In the Trial of indomethacin prophylaxis 999 ELBW babies were included [4]. They were divided into 2 groups - with and without PDA and further into 2 subgroups each (treated with indomethacin 0.1 mg/kg per dose every 24 hours for three days or with placebo).

52% (55/105) of the babies with PDA who were treated with indomethacin had BPD versus 56% (137/246) after placebo. The incidence of the pulmonary complication by the patients without PDA was 43% (170/391) after indomethacin and 30% (78/257) after placebo.

The results of the logistic regression analysis showed that indomethacin treatment is associated with higher risk for BPD by infants without PDA due to weight loss and increased need for supplemental oxygen. The risk/benefit ratio of this strategy is not favorable since spontaneous ductal closure would have taken place by 40% of the babies. Therefore, they were unnecessarily exposed to adverse drug effects.

Another approach is to give medications only by symptomatic infants with PDA (rescue therapy). Ibuprofen is as effective as indomethacin - the rate of successful ductal closure after treatment with one of these COX-inhibitors varies between 75 and 93% [5].

There are some differences between the two medications - indomethacin leads to a greater reduction in cerebral blood flow and oxygen consumption compared to ibuprofen [6] and it is supposed that this action is associated with prevention of IVH by premature infants [7]. However, indomethacin is associated with reduction of renal blood flow and increase in serum creatinine levels compared to ibuprofen, resulting in significant oliguria and elevation of serum creatinine levels.

Ibuprofen has less nephrotoxicity and lower incidence of NEC but is associated with higher risk of pulmonary complications. Ibuprofen can be given orally with efficacy comparable to intravenous administration.

Peroral paracetamol has similar efficacy and safety as the COX-inhibitors for the closure of PDA by premature neonates [8]. The results from a prospective study have demonstrated that the rate of ductal closure with paracetamol is similar to indomethacin and ibuprofen but the safety profile of paracetamol is better, with less adverse events regarding the renal function, platelet count, and gastro-intestinal bleeding [9].

Interventional closure of PDA

Device closure of PDA has been limited mainly to patients weighting > 4 kg but recently Backes., *et al*. have reported on percutaneous closure of PDA by 52 very preterm infants with median of 2.9 kg (range 1.2 - 3.9 kg) over the course of 10 years [10]. 69% had received medical treatment for PDA closure before they were referred for intervention. The reasons for referral were: prolonged need for respiratory support, echocardiographic evidence for volume overload of the left ventricle, failure to thrive, concerns for pulmonary hypertension.

The procedure was successful by 88% of the babies among which was the patient with the lowest weight - 1.2 kg. The most common adverse events were associated with arterial injury and were observed by one third of the patients. However, there was no association between the incidence of these complications and the weight of the infant at the time of the procedure. According to the authors the intervention led to improvement of the respiratory status and contributed to faster weaning form the ventilator.

As the indications for percutaneous ductal closure are not well defined and there were great differences in patient characteristics in the current study there is a need for randomized controlled trials assessing the risk/benefit ratio of this approach.

Surgical ligation of PDA

The first operative ligation of PDA was performed in Boston almost 70 years ago. Recently this procedure is rarely a treatment method of choice and is used as last option only in selected cases when the clinical symptoms of the hemodynamically significant PDA are intractable, by pending complications and when all other conservative measures have failed.

Although the intervention leads to definitive closure of PDA it has a lot of disadvantages: need for thoracotomy, risk for pneumothorax, chylothorax, scoliosis and infection [11]. Furthermore, surgical PDA ligation by babies with birth weight </=1000 g is associated with vocal cord paralysis [12,13], as well as need for postoperative inotropic support due to profound hypotension [14]. There are data indicating that early ductal ligation is an independent risk factor for BPD and may disturb normal lung growth [15,16]. Ductal ligation may be associated with adverse neurodevelopmental outcomes [17]. It is possible that the above mentioned complications neutralize the benefits of eliminating the left-to right ductal shunt.

Jhaveri., *et al*. have compared early surgical ligation with conservative approach by premature infants </= 27 weeks of GA [18]. The initial strategy at their institution was to stop feedings and ligate all ducts which failed to close after indomethacin treatment. At the second stage the researchers assumed a less aggressive strategy with continuing feedings and ligating the ducts only by signs of cardiopulmonary compromise. All infants in both periods received prophylactic indomethacin therapy.

The results showed that the conservative approach was associated with lower rates of duct ligation (72 vs 100%; $p < 0.05$), without significant differences in the rates of complications (BPD, sepsis, retinopathy of prematurity, neurologic injury, and death) and with lower incidence of NEC compared to the patients with early surgical treatment.

Treatment vs. expectant management

There is evidence that spontaneous closure of PDA by infants born preterm can find place at the age of several months [19]. The results of several observational studies assessing premature infants with PDA show that the rate of spontaneous closure of the DA by the end of the first postnatal week by babies with birth weight < 1000g varies between 31 and 34% [20].

Such findings raise some questions: Is treatment of PDA actually needed? Isn't treatment of PDA by premature newborns associated with more harms than benefits? It seems that it is crucial to make a difference between patent arterial duct and hemodynamically significant arterial duct. The patency of DA may be a significant source of additional blood flow to the not yet fully developed lungs of the premature infant [21].

Furthermore, the benefits of ductal closure - either medically or surgically, are not proven. Up to this moment there is not enough evidence that eliminating the left-to-right shunting through the arterial duct is associated with improvement of CLD. The results of one study show that early surgical ligation of PDA does not contribute to reduction of the rate of NEC by babies with birth weight < 1000g [22].

In a large prospective Australian study including 2701 preterm infants born < 29 gestational weeks 58% of the babies needed no treatment of the PDA; 37% were given medications for ductal closure and by 4.6% of the participants the arterial duct was surgically ligated [23].

The results of the multivariate regression analysis showed that the infants by whom the PDA was treated either surgically or medically had worse outcomes - developmental delay, hearing loss, and motor impairments. The authors conclude that it is probably better to be more conservative and utilize expectant strategy by premature babies with PDA.

The aim of the international PDA-TOLERATE trial was to assess the effect on neonatal morbidity of early routine treatment of PDA vs. expectant management and treatment by certain indications by babies born before GA of 28 weeks (n = 202) [24].

The participants in the ERT received indomethacin, ibuprofen or paracetamol. As the efficacy of these three drugs on ductal closure is similar each center was free to choose which one to use. In the conservative treatment group initially no medication was given and the babies were just observed. Echocardiogram was performed between days 7 and 10 after the start of the study.

The results showed that ERT was not associated with any benefits - it did not reduce neither the number of PDA ligations nor the incidence of PDA upon leaving the hospital. On the contrary, compared to conservative strategy, early treatment led to higher rate of unfavorable outcomes - delayed feeding, greater number of babies with late-onset neonatal sepsis as well as higher mortality by infants with gestational age >/=26 weeks.

In the multicentre, randomized European BeNeDuctus trial early treatment (24 - 72h postnatal age) with ibuprofen is being compared with no treatment (conservative strategy) by preterm infants (GA < 28 weeks) with diagnosed on echocardiography PDA with diameter >1.5 mm [25]. The primary outcome is the composite of mortality, and/or NEC, and/or BPD. Secondary outcome measures include heart failure, comorbidity and adverse events during the hospital stay and long-term neurodevelopmental outcome assessed at a corrected age of 2 years.

The results of this study are being expected and when known, will shed more light on the risk/benefit ratio of expectant management, and will probably change the way premature infants with PDA are being treated.

Conclusion

Based on data which we have up to this moment, the decision to treat or not to treat the PDA needs to be individualized for every neonate. The clinician has to take into account the patient characteristics, comorbidities and other circumstances including the possibilities of the neonatology clinic taking care of the baby for active observation and adjustment of the therapeutic strategy in case of deterioration of the clinical status.

Conflict of interest

We have no conflicts of interest to declare.

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Volume 6 Issue 10 October 2019